REMARKS

Claims 15-19 are pending.

The rejections under 35 U.S.C. §103(a)

Claims 15-19 were rejected for obviousness over WO 00/53192 in view of Bedi et al., 2003, Critical care Medicine 31:2470-2477 (Bedi) and Hasselgren et al., 1986, Intensive Care Medicine 12:13-16 (Hasselgren).

The Applicants respectfully traverse this rejection for the following reasons:

At most, the abstract of Bedi has been shown to be prior art

The present application claims priority from European patent application No. 03024201.0, filed on October 21, 2003. See top of page 3 of the enclosed copy of European patent application No. 03024201.0 (Exhibit A) where the following appears: "Date of filing: 21.10.03." This European patent application contains essentially the same disclosure as the PCT application for which the present application is the U.S. national phase. The present claims thus are therefore entitled to an October 21, 2003 effective filing date.

The Applicants obtained a copy of Bedi bearing a date stamp from the Weston Library at the University of Wisconsin which indicates that Bedi was received by that library on October 22, 2003 (see Exhibit B).

In an Examiner Interview Summary placed into the record by the Examiner on October 14, 2009 (Exhibit C), the Examiner stated: "It was determined by the Office (STIC search) that

the reference of Bedi et al. Crit Care Med was entered into PubMed on 10/8/03 (see page 2 of 2 of the attachment underlined in red) and is therefore prior art."

The portion of Bedi that appears in the attachment to Exhibit C and was referred to by the Examiner as having been "entered into PubMed on 10/8/03" is the abstract of Bedi.

In view of Exhibits A-C and the remarks above, the Applicants submit that the present record establishes, at most, that the abstract of Bedi, and not the entire contents of Bedi, is prior art to the present application.

Neither Bedi nor Hasselgren can be combined with WO 00/53192 to arrive at the presently claimed invention

Bedi

The Examiner argued that the present claims are obvious because WO 00/53192 teaches the use of xenon to treat neurointoxications and, although WO 00/53192 does not teach the specific use of xenon recited in the present claims, i.e., to reduce apoptotic cell death in endothelial cells of the intestine in sepsis, Bedi and Hasselgren provide this missing disclosure. See the Office Action, page 3: " '192 [WO 00/53192] broadly teaches the use of xenon or xenon gas mixtures for treating neurointoxications ..." See also the Office Action, page 4:

> 1. The difference between the instant application and '192 is that '192 do not expressly teach a method of reducing apoptotic cell death in endothelial cells of the intestine in sepsis. This deficiency in '192 is cured by the teachings of Bedi et al. and Hasselgren et al.

The Applicants respectfully traverse this rejection because one of ordinary skill in the art would not combine Bedi or Hasselgren with WO 00/53192.

As discussed above, at most the abstract of Bedi is prior art. The abstract of Bedi, as shown in Exhibit C, reads as follows:

AB - OBJECTIVE: Many sedative regimens are used in the intensive care setting, but none are wholly without adverse effect. Xenon is a noble gas with sedative and analgesic properties. It has been used successfully as a general anesthetic and has many desirable properties, not least of which is a minimal effect on the myocardium. In theory, xenon may provide sedation without adverse effect for certain groups of critically ill patients. The objective of this study was to assess the feasibility of using xenon as an intensive care sedative. DESIGN: Double-blind, randomized study. SETTING: Tertiary-level intensive care unit. SUBJECTS: Twenty-one patients admitted to an intensive care unit following elective thoracic surgery. INTERVENTIONS: A standard intensive care sedation regimen (intravenous propofol at 0-5 mg.kg-1.hr-1 and alfentanil 30 microg.kg-1.hr-1) was compared with a xenon sedation regimen delivered using a novel bellows-in-bottle delivery system.MEASUREMENTS AND MAIN RESULTS Each sedative regimen was continued for 8 hrs. The hemodynamic effects, additional analgesic requirements, recovery from sedation, and effect on hematological and biochemical variables were compared for the two sedation regimens. All patients were successfully sedated during the xenon regimen. The mean +/- SD end-tidal xenon concentration required to provide sedation throughout the duration of the study was 28 +/- 9.0% (range, 9-62%). Arterial systolic, diastolic, and mean pressures showed a greater tendency for negative gradients in patients receiving the propofol regimen ($p < .05$, $p < .1$, and $p < .01$, respectively). Recovery following xenon was significantly faster than from the standard sedation regimen ($p < .0001$). Hematological and biochemical laboratory markers were within normal clinical limits in both groups. CONCLUSIONS: Xenon provided satisfactory sedation in our group of patients. It was well tolerated with minimal hemodynamic effect. Recovery from this agent is extremely rapid. We have demonstrated the feasibility of using xenon within the critical care setting, without adverse effect.

AD - Royal Group of Hospitals, Belfast, Northern Ireland.

The abstract of Bedi makes no mention of sepsis. Thus, one of ordinary skill in the art could not have combined Bedi with WO 00/53192 in order to remedy the lack of disclosure in WO 00/53192 of the use of xenon to treat sepsis.

Hasselgren

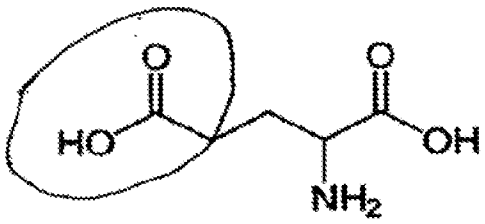
According to the Office Action, motivation to combine Hasselgren with WO 00/53192 supposedly arises because WO 00/53192 is directed to treating neurointoxications resulting from

increased brain levels of neurotransmitters such as glutamate and Hasselgren teaches that sepsis involves increased glutamate levels. Therefore, one of ordinary skill in the art would understand that sepsis is a condition that causes neurointoxications and thus can be treated by the methods of WO 00/53192. See page 5 of the Office Action:

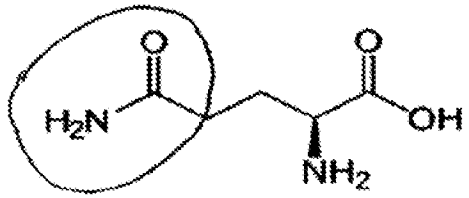
> One of ordinary skill in the art would have been motivated to do this because '192 teaches treating neurointoxications and points out glutamate as a neurotransmitter. Hasselgren et al teaches that the septic condition caused increased glutamate levels which would be a neurointoxication as taught by '192 and thus within the scope of '192.

However, Hasselgren would not be combined with WO 00/53192 because Hasselgren makes no mention of glutamate. Hasselgren does state that brain glutamine levels may be increased in sepsis. But glutamate and glutamine, although amino acids having similar names, have significantly different chemical structures: glutamate has an acidic side chain while glutamine has a basic side chain. See the circled portion of the structures of glutamate and glutamine below.

glutamate



glutamine



Furthermore, Hasselgren is very tentative about its conclusions. See page 13, left column: "[T]he available evidence is preliminary and might be easily contested."

WO 00/53192 states that its methods are applicable when there is "neurotransmitter excess, particularly of glutamate, noradrenalin and/or dopamine." Rather than teaching that brain neurotransmitter levels in general are in excess in sepsis, Hasselgren instead expresses doubt that neurotransmitters in general are in excess in sepsis by raising the possibility that there may be decreased synthesis of neurotransmitters in sepsis. See page 13, right column: "It is entirely possible that that there may be decreased synthesis of peptides or other neurotransmitters in septic encephalopathy."

Elsewhere, Hasselgren states that some neurotransmitters are elevated, some are not. See page 15, right column:

> Increased brain concentrations of the serotonergic and reduced levels of the catecholaminergic neurotransmitters, along with the occurrence of false neurotransmitters, may be important factors in the pathophysiology of septic encephalopathy.

With respect to noradrenaline (also known as norepinephrine), Hasselgren teaches that the level of this neurotransmitter is reduced. See page 14, right column: "[T]he levels of the catecholaminergic neurotransmitters norepinephrine, …[others listed] …are reduced."

Hasselgren also teaches that the effects of noradrenaline and dopamine in the brain are blocked by other substances in sepsis. See page 15, left column: "[These substances] are weak or 'false' neurotransmitters which displace norepinephrine as well as dopamine and epinephrine from neural synaptosomes."

Thus, Hasselgren teaches away from using the methods of WO 00/53192 in sepsis. Upon reading Hasselgren, one of ordinary skill in the art would have been deterred from using the methods of WO 00/53192 for sepsis because WO 00/53192 teaches that its methods are applicable in conditions where there is too much activity from noradrenalin and dopamine and Hasselgren teaches that there is less activity from noradrenalin and dopamine in sepsis.

In view of the above, it is respectfully requested that this rejection be withdrawn.

The Applicants hereby make a Conditional Petition for any relief available to correct any defect seen in connection with the filing of this paper, or any defect seen to be remaining in this application after the filing of this paper. The Director is authorized to charge Kenyon & Kenyon's Deposit Account No. 11-0600 for the Petition fee and any other fees required to effect this Conditional Petition.

Respectfully Submitted,

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